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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/851,230	05/08/2001	John Hamilton	111590-121 (US2)	4015

28089 7590 05/06/2004

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EXAMINER	
BELYAVSKYI, MICHAIL A	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/851,230	HAMILTON ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-27 and 29-35* is/are pending in the application.

4a) Of the above claim(s) *14-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed on 12/29/03 is acknowledged.

Claims 14-27, 29-35 are pending.

Applicant's election with traverse of Group III, claims 1-7, now claims 29-35 in Response to Restriction Requirement, filed on 12/29/03 is acknowledged. Applicant traverse the Restriction Requirement on the grounds that the search of Groups III and VI and IX together would not constitute a serious search burden on the examiner and that search of the claims of Group III would provide useful information for the claims of Group VI and Group IX

This is not found persuasive because the MPEP 803 (August 2001) states that "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search". The Restriction Requirement enunciated in the previous Office Action meets this criteria and therefore establishes that serious burden is placed on the examiner by the examination of more than one Group. The Inventions are distinct for reasons elaborated in paragraphs 3-5 of the previous Office Action and above

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 14-27 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claims 29-35 are under consideration in the instant application.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

4. The following is a quotation of the second paragraph of 35 U.S.C. 112.
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 35 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Dependent claim 35 recites the limitation " other inflammatory mediators". There is insufficient antecedent basis for this limitation in the claim, since the base claim 34 does not recites "inflammatory mediators". Also an issue is that the characteristics and metes and bounds of "other inflammatory mediators" are unclear , indefinite, and not defined by the specification as filed.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for ameliorating the effects of inflammation in a subject which comprises administering one or more antibodies against M-CSF or GM-CSF and further comprises administering an antibody which antagonizes the effects of u-PA does not reasonably provide enablement for a method for ameliorating the effects of inflammation in a subject which comprises administering one or more antibodies against M-CSF or GM-CSF and further comprises administering *any agent* which antagonizes the effects of u-PA or *any* agent which antagonizes the effects of *any other* inflammatory mediators. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation.

(A) The claims as written encompass the genus of agent which antagonizes the effects of uPA and other inflammatory mediators. The genus encompasses peptides wherein such peptides have numerous differences in amino acid sequences.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

Applicant discloses using anti-u-PA antibodies in addition to administering one or more antibodies against M-CSF or GM-CSF to be used in a method for ameliorating the effects of inflammation in a subject (see entire document, page 14 in particular). Applicant has not taught how to make and/or use any agent which antagonizes the effects of u-PA or *any* agent which antagonizes the effects of *any other* inflammatory mediators. The structural and functional characteristics of said any agents and any inflammatory mediators are not defined in the claim s and in the specification.

Since the instant fact pattern fails to indicate that representative number of structurally related compounds is disclosed, the artisan would not know the identity of a reasonable number of representative compounds falling within the scope of the instant claims and consequently would not know how to make them. An assay for *finding* a product is not equivalent to a positive recitation of *how to make* a product.

Moreover, there is no disclosure in the Specifications of *any other inflammatory mediators,* the effects of which should be antagonized in a method for ameliorating inflammation. The is no guidance in the specification with regard to whether " *any other inflammatory mediators*" refer to mediators defined as belonging to the same species because they share a common function or because they share common structural elements. Applicant has not exemplified *in vivo* studies *any* agent which antagonizes the effects of *any other* inflammatory mediators that were used for ameliorating the effects of inflammation . Using *any* agent which antagonizes the effects of *any other* inflammatory mediators" does not necessarily ensure its ability to fulfill the claimed function. Moreover, US Patent 5,962,477 teaches that inflammatory diseases is a complex of cellular and molecular events and it has been recognized that various mediators are acting differently and some times not in parallel. Moreover, administering antibodies to some inflammatory mediators do not produced the required therapeutic effects (see entire document, column 2 and overlapping columns 11 and 12 in particular).

In addition, protein chemistry is probably one of the most unpredictable areas of biotechnology . It is known in the art that even single amino acid changes or differences in a proteins amino acid sequence can have dramatic effects on the protein's function. For example, Mikayama et al. (PNAS, 1993. 90: 10056-10060) teach that the human glycosylation factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (see Figure 1 in particular). Yet, Mikayama et al. further teach that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF activity (see Abstract in particular).

Burgess et al (J Cell Biol. 111:2129-2138, 1990) show that a conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited.

Applicant has not provided sufficient biochemical information (e.g. structural characteristics, amino acid composition , physicochemical properties, etc) that distinctly identifies such "agents" other than antibodies that binds specifically to u-PA that can be used in the method for ameliorating the effects of inflammation. While any "agents " may have some notion of the activity of the "antibodies which antagonizes the effects of u-PA", claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make such agents, commensurate in scope with the claimed invention. Since the instant fact pattern fails to indicate that representative number of structurally related compounds is disclosed, the artisan would not know the identity of a reasonable number of representative compounds falling within the scope of the instant claims and consequently would not know how to make them.

Applicant is relying upon certain biological activities and the disclosure of a single species to support an entire genus. It is well known that minor structural differences among even structurally related compounds or compositions can result in substantially different biology, expression, and pharmacology of proteins. Therefore, structurally unrelated any agent which antagonizes the effects of u-PA or any agent which antagonizes the effects of any othe inflammatory mediators , encompassed by the claimed invention other than "antibody which antagonizes the effects of u-PA" would be expected to have greater differences in their activities.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method for ameliorating the effects of inflammation in a subject which comprises administering one or more antibodies against M-CSF or GM-CSF and further comprises administering *any agent* which antagonizes the effects of u-PA or *any* agent which antagonizes the effects of *any other* inflammatory mediators in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

8. Claims 29-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of : a method for ameliorating the effects of inflammation in a subject which comprises administering one or more antibodies against M-CSF or GM-CSF and further comprises administering an antibody which antagonizes the effects of u-PA.

Applicant is not in possession of : a method for ameliorating the effects of inflammation in a subject which comprises administering one or more antibodies against M-CSF or GM-CSF and further comprises administering *any agent* which antagonizes the effects of u-PA or *any* agent which antagonizes the effects of *any other* inflammatory mediators.

The claimed invention is drawn to a genus of agents, however, structural identifying characteristics of the genus are not disclosed. There is no evidence that there is any *per se* structure/function relationship between the disclosed agent compound and any others that might be found using the claimed method to be used in a method for ameliorating the effects of inflammation in a subject.

A description of what a material does rather than of what it is, usually does not suffice. The patent does not more than describe the desired function of the compound called for and contains no information by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention. At best, it simply indicates that one should run tests on a wide spectrum of compounds in the hope that at least one of them will work. Inadequate written description that merely identifies a plan to accomplish an intended result "is an attempt to preempt the future before it has arrived" *Fiers v. Revel*, 984 F.2d 1164,1171 9Fed.Cir. 1993).

Applicant has disclosed a limited number of species; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequences themselves are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

A description of a genus of agents may be achieved by means of a recitation of a representative number of polypeptide sequences, defined by amino acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.
Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:
A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 37(c) of this title before the invention thereof by the applicant for patent.

10. Claims 29-33 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 00/09561 or by JP 2000198799.

WO'561 teaches a method for ameliorating the effects of inflammation in a subject, comprising administering an antibodies against GM-CSF (see entire document, Abstract and page 6 in particular). WO'561 teaches that administering said antibodies would antagonized the effects of GM-CSF on macrophages (see overlapping pages 6 and 7 in particular). WO'561 teaches that said antibodies are identified by a product screening (see pages 8, 15 and 22 in particular).

JP '799 teaches a method for ameliorating the effects of inflammation, comprising administering antibodies against GM-CSF (see entire document, Abstract and pages 5, 7 and 22 in particular). JP '799 teaches that said antibodies are identified by a product screening (see overlapping pages 8-9 in particular).

Claims 30 and 33 are included because the claimed functional limitation would be inherent properties of the referenced antibodies against GM-CSF, because the claimed method for ameliorating the effects of inflammation and the referenced method using the same antibodies against GM-CSF. Under the principles of inherency, if a prior art method, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art. When the prior art method is the same as a method described in the specification, it can be assumed the method will inherently perform the claimed process. See MPEP 2112.02.

The reference teachings anticipates the claimed invention.

11. Claims 29-33 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 5,837,460.

US Patent '460 teaches a method for ameliorating the effects of inflammation, comprising administering antibodies against GM-CSF (see entire document, Abstract and columns 5 and 9 in particular). US Patent '460 teaches that in some embodiments, a method for amelioration the effects of inflammation in a subject comprises administering antibodies to different inflammatory mediators (see column 5, lines 35-43 in particular). US Patent '460 teaches that said antibodies are identified by a product screening (see column 6 and overlapping columns 14-15 in particular).

Claims 30 and 33 are included because the claimed functional limitation would be inherent properties of the referenced antibodies against GM-CSF, because the claimed method for ameliorating the effects of inflammation and the referenced method using the same antibodies against GM-CSF. Under the principles of inherency, if a prior art method, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art. When the prior art method is the same as a method described in the specification, it can be assumed the method will inherently perform the claimed process. See MPEP 2112.02.

The reference teaching anticipates the claimed invention.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/09561 or by JP 2000198799 or US Patent 5,837,460 each in view of US Patent 5444153 or Us Patent 5662609.

The teachings of WO 00/09561 or JP 2000198799 or US Patent 5,837,460 have been discussed, supra.

The claimed invention differs from the reference teaching in that the WO 00/09561 , JP 2000198799 and US Patent 5,837,460 do not teach a method for ameliorating the effects of inflammation in a subject comprising administering antibodies against GM-CSF and further administering an agent which antagonizes the effects of u-PA and an agent which antagonizes the effects of other inflammatory mediators.

US Patent '153 teaches a method of treating inflammatory diseases in patients comprising administering specific inhibitors of u-PA (see entire document, Abstract column 2 and column 5, lines 55-65, and column 6 in particular).

US Patent '609 teaches a method of treating inflammatory diseases in patients comprising administering specific inhibitors of u-PA or inhibitors of agents which inhibits the effects of inflammatory mediators (see entire document, column 4 and column 6 in particular).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent '153 or US Patent '609 to those of WO 00/09561 or JP 2000198799 or US Patent 5,837,460 to obtain a claimed method for ameliorating the effects of inflammation in a subject comprising administering antibodies against GM-CSF and further administering an agent which antagonizes the effects of u-PA and an agent which antagonizes the effects of other inflammatory mediators.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because agent which antagonizes the effects of u-PA and an agent which antagonizes the effects of other inflammatory mediators can be used in the a method of treating inflammatory diseases as taught by US Patent '153 or US Patent '609 and can be combined with a method of treating inflammatory diseases in patients taught by WO 00/09561 or JP 2000198799 or US Patent 5,837,460. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. No claim is allowed.

14. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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May 3, 2004

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